

Change(s) applied
to document,

Page 80, line 10, please replace the paragraph thereat as follows:

Example 1. Synthesis of Retinol Binding Protein Receptor Protein in Human Keratinocytes and Psoriatic Plaques

Anti-human retinol binding protein receptor peptide antibody is generated as follows. A cDNA corresponding to the retinol binding protein receptor expressed in humans (GenBank Accession Number NM_000329) is used as basis for the design of a 9 amino acid peptide. The peptide has the following sequence: VNGATAHNNH. (SEQ ID NO: 8)

Page 83, line 19, please replace the paragraph thereat as follows:

Generation of Keratin 1 DNA Probe

A sequence of the human K1 cDNA (1046-1630) was amplified by PCR (*Pfu* Polymerase 35 cycles) using primers 5'-GCATCATTGCTGAGGTCAAGGC-3' (SEQ ID NO: 9) and 3'-CACCTCCAGAACCATAGC-5'. (SEQ ID NO: 10) This sequence was cloned into JM109 cells (Promega) using PCR-Script Amp Cloning Kit (Stratagene) and cells scaled up in LB Broth. The plasmid DNA was extracted from the JM109 cells using HiSpeed Plasmid Midi Kit (QIAGEN). The probe sequence was cut out using BamH1 and SacII restriction Enzymes (Promega). The DNA was run on a 1.5% Agarose gel, cut out and purified using QIAexII Gel Extraction Kit (QIAGEN).

Page 91, line 1, please replace the paragraph thereat as follows:

Amino acids are numbered as in Cowan et al., *Proteins: Structure, Function and Genetics* 1990:8, p. 44-61. Peptides 589 (*Gly-Arg-Val-Arg-Leu-Leu-Asn-Asn-Trp-Asp-Val-Cys-Ala*) (SEQ ID NO: 11) and 592 (*Met-Lys-Tyr-Trp-Gly-Val-Ala-Ser-Phe-Leu-Gln-Lys-Gly-Asn-Asp*) (SEQ ID NO: 12) are synthesised to mimic the proposed binding regions of RBP to its receptor, by Arthur Moir, University of Sheffield.

Page 110, line 1, please replace the paragraph thereat as follows:

Standard protocols for PCR are used to generate probes to analyze differentiation status. Probes are made against K1, K10 and CRABP II, using the following primer pairs:

K10

Primer sense 726-743

Primer antisense 1257-1278

TGGAGGCTGACATCAACG (SEQ ID NO: 13)

TATTCAGTATTCTGGCACTCGG (SEQ ID NO: 14)

Page 32, line 22, please replace the paragraph thereat as follows:

A4
The Peroxisome Proliferator-Activated Receptor (PPAR) Response Element has a sequence AGGTCA [1bp spacer] AGGTCA (SEQ ID NO: 5), and is involved in regulation of expression of genes including cyclooxygenase (COX2), cytosolic phospholipase A2 (CPLA2), mitochondrial fatty acid beta-oxidising enzymes, ABCA1, ARE6, ARE7, GLUT2. Examples of disorders associated with abnormal, ectopic or over-expression of PPAR response element mediated genes include arteriosclerosis, rheumatoid arthritis, inflammatory bowel disease, obesity, hypertension, diabetes, hyperlipidemia, colon cancer.

Change(s) applied
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4/
Page 33, line 5, please replace the paragraph thereat as follows:

A.C.
5/23/2011
Thyroid Response Element

A5
The thyroid response element has a consensus sequence 5'-AGGTCA [4bp spacer] AGGTCA -3' (SEQ ID NO: 6), and is involved in regulation of expression of a variety of genes, including connexin43, hyperpolarization-activated cyclic nucleotide-gated channel gene (HCN2), C/EBPalpha, prohormone convertases (PC1) and (PC2), Purkinje cell protein (Pcp-2), Calbindin, Myo-inositoltriphosphate (IP-3) receptor, Neurotrophin-3 (NT-3), Nerve growth factor (NGF), Brain-derived neurotrophic factor (BDNF), Neurotrophin 4/5, Reelin, Neural cell adhesion molecule (NCAM), Tenascin-C, Srg1, Hairless, BCL-2, Myelin basic protein (MBP), pro-alpha1(I) collagen, uncoupling protein 3 (UCP3), medullary thyrotropin-releasing hormone (TRH), beta-amyloid precursor protein (APP), fatty acid synthase promoter, malic enzyme, steroid receptor coactivator-1 (SRC-1), sodium, potassium-adenosine triphosphatase alpha3, apolipoprotein CII and lipocalin-type prostaglandin D synthase (beta-trace), among others.

Page 34, line 7, please replace the paragraph thereat as follows:

A6
Diseases which may be treated by the methods and compositions described here include those involving over-expression, ectopic expression, or abnormal expression for other response elements including COUP-TR (chicken ovalbumin upstream promoter transcription factor II). Diseases associated with such expression from COUP-TR include Type I mature onset diabetes of the young (MODY1); genes which are under the control of this response element include hepatocyte nuclear factor 1. The chicken ovalbumin upstream promoter transcription factor II response element has a sequence AGGTCA [1bp spacer] AGGTCA (SEQ ID NO: 7).

cover the required fee for a small entity. The Commissioner is hereby authorized to charge any other fees occasioned by this paper, or credit any overpayment in fees, to Deposit Account No. 50-0320.

AMENDMENT

It is respectfully requested that the application be amended, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel, as follows:

IN THE SPECIFICATION:

Page 27, line 19, please replace the paragraph thereat as follows:

A1
Preferably, the nuclear receptor is one which interacts with its cognate response elements as a heterodimer with the retinoid X receptor (RXR). Thus, preferably, the nuclear receptor is one which forms a heterodimer, preferably with the retinoid X receptor, and is capable of recognising a response element in which two AGGTCA (SEQ ID NO: 23) binding sites are arranged in tandem. Preferably, binding and recognition is capable of causing modulation of gene expression of a gene linked to the response element. The response element may be in any control region of a gene, for example, in an upstream control region such as a promoter or enhancer. Target selection by the complexes requires the spacing between the binding sites to act as the identity element.

Page 30, line 15, please replace the paragraph thereat as follows:

A2
An example of a retinoic acid response element (RARE) is the sequence AGGTCA [5bp spacer] AGGTCA. (SEQ ID NO: 1) Another example of a retinoic acid response element is the DR-2 RARE with the sequence AGGTCA [2bp spacer] AGGTCA. (SEQ ID NO: 2)

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Page 31, line 10, please replace the paragraph thereat as follows:

A.C./ *Vitamin D Response Element*

5/23/2011
A3
The consensus Vitamin D Response Element (VDRE) has the following sequence:
GGGTGA NNG GGGGCA. (SEQ ID NO: 3) Another example of a vitamin D response element is the sequence AGGTCA [3bp spacer] AGGTCA. (SEQ ID NO: 4)

Page 56, line 19 to page 57, line 4, kindly rewrite the paragraph thereat to read as follows:

Thus, any of the above conditions may be treated or alleviated by the methods and compositions described here. In particular, the methods and compositions described are useful for treating any tumour, carcinoma, etc, which has been treated successfully or unsuccessfully with retinoid therapy. The methods and compositions are also useful to treat pre-malignant conditions i.e. to prevent their progression to actual malignancy. Reduction in endogenous retinoic acid levels inhibits angiogenesis, and therefore such reduction may be used to prevent the spread of tumours. In particular, such reduction in endogenous retinoic acid levels may be achieved by antagonising the retinol binding protein receptor, preferably in such a way as to prevent retinol binding protein and/or retinol uptake. Reduction in endogenous retinoic acid levels may also be achieved by inhibiting or preventing synthesis of retinoic acid, by for example, inhibiting a retinoic acid synthesis enzyme as described elsewhere in this document. Specific examples of tumours include ~~include~~ melanocytic naevus and mrelodysplastic syndrome.

Change(s) applied
to document,
/A.C./
5/23/2011

58
Page 57, lines 10 to 16, kindly rewrite the paragraph thereat to read as follows:

The common medical meaning of the term “neoplasia” refers to “new cell growth” that results as a loss of responsiveness to normal growth controls, e.g. to neoplastic cell growth. A “hyperplasia” refers to cells undergoing an abnormally high rate of growth. However, as used herein, the terms neoplasia and hyperplasia can be used interchangeably, as their context will reveal, referring to generally to cells experiencing abnormal cell growth rates. Neoplasias and hyperplasias include “tumors,” which may be either benign, premalignant or malignant.

Page 76, line 17, to page 80, line 9, kindly rewrite the paragraph therat to read as follows:

Paragraph 1. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises administering to the patient an antagonist of a retinol binding protein receptor (RBPr).